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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/889,331	12/18/2001	Andrew A. Young	030639.0031,UTL1	2765

28381 7590 01/29/2004

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EXAMINER	
LIU, SAMUEL W	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 01/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/889,331	YOUNG ET AL.	
	Examiner	Art Unit	
	Samuel W Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2003 and 17 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-43* is/are pending in the application.

4a) Of the above claim(s) *none* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1-29-02* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the claims

Claims 21-43 are pending.

A request (filed 2 December 2003) for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed 17 November 2003 has been entered.

Applicants' amendment filed 17 November 2003, which cancels claims 1-20 and adds new claims 21-42, and applicants' requests for extension of time of one month (filed 17 November 2003 and filed 24 November 2003) have been entered.

Therefore, the pending claims 21-43 are under examination in this Office action.

IDS

The references listed in IDS filed 29 January 2002 have been received and considered. The examiner-initialed copies of the PTO-1449 form of this IDS are enclosed with this Office action.

Specification Objection

The disclosure is objected to because of the following informalities:

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 21-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21 recites "more than 30 amino acid residues in length"; the recitation is unclear as to what is the upper limit of the said length; does the claimed amino acid sequence is a fusion polypeptide? Claim 21 recites "an exendin"; the recitation is ambiguous as to whether or not said exendin refers to exendin-1, or exendin-2 or exendin-3 or exendin-4 (note that these exendin peptides are structurally or/and functionally diverse. Claim 21 recites "therapeutic lowering of plasma glucagon". Because the specification does not define the phrase 'therapeutic lowering", such the recitation is unclear as to whether or not therapeutic lowering refers to *in vivo* lowering process or a drug treatment associated process wherein the lowering plasma glucagon is not a sole mechanism for said treatment but a part of the treatment. See also claims 33 and 39. Claim 21 is also indefinite as to the recitation "exendin analog" because the specification provides no definition of it and because the recitation is unclear regarding whether or not the exendin analog encompasses exendin agonist, antagonist or/and chemically modified exendin, e.g., PEG-conjugated exendin molecule. In addition, claim 21 recites "an exendin, an exendin analog or combination thereof"; the recitation is not apparent as to whether or not the combination refers to combination between exendin and the exendin analog(s) or between exendin analogs; what is the

ratio of exendin versus the exendin analog(s)? See also claims 28, 33 and 39. The dependent claims are also rejected.

Claim 31 is indefinite because the claim appears to contain an open-ended Markush group. See the recitation of "or naphthylalanine". Markush language requires close language. See also claim 40 recitation "or N-alkylalanine", and claim 42 recitation "or naphthylalanine" and "or N-alkylalanine"; these recitations are the open-ended Markush languages.

Response to the rejection under 35 USC 112, the second paragraph

The response filed 17 November 2003 asserts that the recitation "exendin analog" is clear and definite as the specification, including incorporated documents, make clear that exendin analog may be a subset of agonist and the skilled artisan would be apprised of the scope of the recitation (see page 8, the last paragraph, and page 9). The applicants' argument is unpersuasive because no where in the specification has clearly defined the "exendin analog" (note that the incorporated documents cannot substitute the specification description of what is the exendin analog thereof and which applicants regard as the invention, and because said analog would encompass exendin agonist, antagonist or/and chemically modified or/and genetic-engineeringly produced exendin variants.

The response commends that the recitation 'therapeutic lowering of plasma glucagon" in claims 1 and 33 is not indefinite as the skilled artisan will readily understand that the recitation refers to administering to a subject a therapeutically effective amount of drug to achieve lowering the in vivo plasma glucagon level (page 9, the 1st paragraph), and asserts that the specification (pages 11 and 18) has describes the recitation thereof. The applicants' argument is

not persuasive because the specification does not define said recitation and because of the reason set forth in the above rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 27 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification as originally filed does not provide support for the invention as now claimed.

This is a New Matter rejection for the following reasons:

Claim 27 recites the limitation "anti-glucagon agent" which represents a departure from the specification and the claims as originally filed. The instant claim recites the limitation which were not clearly disclosed in the specification and claims as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in the present claims, which did not appear in the specification or original claims, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Claims 21-43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims of the current application recite exendin agonist. Applicant is in possession of a method of lowering plasma glucagon in a subject in need comprising administering to said subject a composition comprising exendin-4 or polyethylene glycol (PEG) conjugated exendin-4 peptide, wherein the subject is suffering from necrolytic migratory erythema (claims 22 and 34) or glucagonoma (claims 23 and 35) or type-2 diabetes (claims 25 and 37). Applicant is not in possession of a method of lowering plasma glucagon in a subject in need comprising administering to said subject a composition comprising (i) any exendin analog encompassing chemically modified analogs, (ii) or recombinantly produced exendin variants, and (iii) any exendin peptide derivatives having amino acid sequence that is more than 30 amino acid residues in length (see claims 1 and 33). There is insufficient written description in the specification with respect to how to make and use the above-mentioned exendin analogs in lowering plasma glucagon in a subject who is suffering from necrolytic migratory erythema or glucagonoma or Type II diabetes.

Exendin is a group of peptide hormone encompassing exendin-1, -2, -3 and –4, which are both structurally and functionally diverse. The current application has only described the method of lowering plasma glucagon in a subject comprising administering to said subject a composition comprising exendin-4 or PEG-conjugated exedin-4, but NOT the method thereof wherein the administered composition comprising any exendin peptide or any exendin peptide with more than 30 amino acid residues or any organic polymer or/and biopolymer conjugate of an exendin peptide. The specification does not provide guidance and working example(s) regarding how to

make and use of the exendin 1 or 2, or analog(s) thereof for treating a condition or a disorder states associated with necrolytic migratory erythema or glucagonoma or Type II diabetes through lowering plasma glucagon level. Thus, the skilled artisan would have not known (*a*) whether or not the both structurally and functionally divergent exendin 1 or 2 or 3 is used as an agonist analog of an exendin, (*b*) how to make and use the conjugate formed between an exendin or the analog of an exendin and a polymer including organic polymer or/and biopolymers (*e.g.*, polynucleotide, polypeptide and mimics thereof, lipid and lipid derivative thereof, and polysaccharide), and (*c*) how to make and use an exendin peptide comprising more 30 amino acids or the analog of said exendin peptide. The specification is silent in description, guidance and working examples in these regards. Thus, applicants are not in possession of a method of lowering plasma glucagon in a subject comprising administering to said subject a composition comprising any exendin analogs or variants as mentioned above.

Applicant has disclosed only exendin-4 or PEG-conjugated exendin-4 for treating a disorder or disease state, e.g., necrolytic migratory erythema or glucagonoma or type-2 diabetes *via* lowering plasma glucagon. Therefore, the skilled artisan cannot envision all the contemplated analogs of an exendin possibilities or any length exendin polypeptides (> 30 amino acid residues) recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description

requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of the analog of an exendin for the claimed method. Thus, Applicant was not in possession of claimed method comprising administering to the subject who is suffering from the disease state the exendin analog (see the above statement). *See University of California v. Eli Lilly and co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

In consideration of the issued stated *supra*, the amount and level of experimentation needed is undue.

Applicants' response to the rejection under 35 USC 112, the first paragraph

The response filed 17 November 2003 asserts that applicants have provides sufficient guidance and working examples as to structural and functional characterization of the claimed exendin analog peptides and assays for their activity in glucagon suppression (see page 8). The applicants' argument is unpersuasive because of the reasons stated above and because the

exendin analog encompasses (i) the exendin variants having varied peptide lengths, (ii) the exendin variants in which amino acid residue(s) is chemically modified, and (iii) the exendin variants conjugated with a polymer (including biopolymers). The "exendin analog" unexpectedly encompasses very broad variants or structural and functional analogs of an exendin; the current disclosure does not describe how to make and use the exendin analog which has a predictable biological activity in lowering plasma glucagon level.

Claim Rejections - 35 USC §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 21-27, 32-38 and 43 are rejected under 35 U.S.C. 102(b) as being anticipated by Eng, J. (US Pat. No. 5424286) as is evidenced by Bloom, S. R. et al. (*Am. J. Med.* (1987) 82 (suppl. 5B), 25-36).

Eng teaches (i) identifying exendin-4 as a pharmaceutical agent, e.g., an insulinotropic agent (see Examples 4-5 and column 2, lines 49-60), (ii) glucagon-like insulinotropic peptide (GLP-1) significantly lowers the plasma concentrations of insulin and glucagon (see column 1, lines 59-62), (iii) in view of treating non-insulin-dependent diabetes mellitus (i.e., Type II diabetes), exendin-4 is more potent than GLP-1 (see column 2, lines 49-64), and (iv)

administering a composition comprising exendin-4 peptide to an individual including human for treating Type II diabetes (see column 2, line 65 to column 3, line 27) via a cellular mechanism, i.e., lowering plasma glucagon *and* insulin concentrations (see column 1, lines 59-63). The Eng's teachings are applied to claims 21, 24-26, 32-33, 36-38 and 43 of the instant application.

Also, Eng teaches administering exendin-4 alone to a patient (see Figure 5 and example 3), as applied to the application claim 27.

Since glucagonoma is characterized as considerably elevated plasma glucagon level and necrolytic migratory erythema is a skin condition of glucagonoma (see page 26 of Bloom et al. reference), the above Eng's teachings are also applicable to claims 22-23 and 34-35 of the current applicantion.

Claims 21-27, 32-38 and 43 are rejected under 35 U.S.C. 102(a) as being anticipated by the reference (*Marketletter*, Published on 24 August 1998, newly cited) as is evidenced by Bloom, S. R. et al. (*Am. J. Med.* (1987) 82 (suppl. 5B), 25-36).

The reference teaches a process of using the identified exendin-4 to inhibit glucagon secretion and clinically treat Type II diabetes patient (human), and clinical trails for using exendin-4. The reference disclosure meets all the limitation of claims 21, 24-27, 32-33, 36-38 and 43 of the instant application. Because glucagonoma is characterized as considerably elevated plasma level of glucagon and necrolytic migratory erythema is a skin condition of glucagonoma (see page 26 of the Bloom et al. reference), the reference anticipates claims 22-23 and 34-35 of the current applicantion as well.

Applicants' response to the reactions under 35 USC 102

The response filed 17 November 2003 asserts that Eng does not teach or suggest ability of exendin-4 suppressing glucagon plasma level (see page 10, the 2nd paragraph). The applicants' argument is unpersuasive because Eng teaches that exendin-4 is more potent than GLP-1 in treating Type II diabetes (see column 2, lines 49-60), and because the exendin-4 treatment of Type II diabetes patient would inevitably lead to suppressing glucagon plasma level. Furthermore, Eng teaches that GLP-1 has ability of lowering both insulin and glucagon plasma concentrations (see column 1, lines 59-63), suggesting that when administering exendin-4 to the patient having a disorder state, e.g., Type II diabetes, the exendin-4 peptide inevitably invoke inhibitory mechanism of glucagon secretion. Note that Type II diabetes associates with elevated plasma glucagon (see Carlsson, A. et al. (2000) *J. Clin. Endocrinol. Metabol.* 85, 76-80, abstract).

The response discusses the issue regarding glucagon secretion suppression and the insulinotropism (i.e., stimulation of insulin secretion), and infers that suppression of glucagon secretion and insulinotropism are not inherently linked and that Eng's teaching with respect to exendin-4 treatment of Type II diabetes does not establish a method of lowering plasma glucagon in a patient in need (see pages 10-11). The applicants' argument is unpersuasive because of the reasons stated above and the following. Eng teaches that (i) insulinotropic GLP-1 has ability of lowering both insulin and glucagon plasma concentrations (see column 1, lines 59-63), and (ii) exendin-4 is more potent than GLP-1 in treating Type II diabetes (see column 2, lines 49-60). The claimed method comprises administering to a subject a composition comprising an exendin wherein lowering plasma glucagon level does not constitute a step pf the

method but rather a mechanism for treating a disorder state, e.g., Type II diabetes. Suppression of plasma glucagon is an inherent property of exendin-4 and GLP-1 peptides. When administered to the patient having Type II diabetes, the exendin would inevitably suppress the plasma glucagon level. Although GLP-1 stimulates insulin secretion (insulinotropic effect), GLP-1 has a potent abililty of inhibiting glucagon scretion; because of this action and GLP-1 insulinotropic effect it has pronounced blood blood glucose lowering effects particularly in patient with Type II diabetes (see column 2, lines 14-18 of US Pat. No. 6268343). This suggests that the insulinotropic agnet, GLP-1, can also act as a potent suppressive agent for glucagon secretion, and that the mechanism of exendin-4 or GLP-1 treatment of Type II diabetes involves supressing glucagon secretion thereby decrease plasma glucagon level. Note that the mechanism of inhibiting glucagon secretion is not known (see column 3, lines 19-22, US Pat. No.6268343). Thus, suppression of glucagon secretion is an inherent mechanism of administering exendin-4 to a patient having a disorder state, e.g., Type II diabetes. Therefore, the Eng's patent anticipates the claimed method of the instant application.

Also, the response assersts that the *Markeletter* reference does no anticiapates the present claims and teach the ability of exendin-4 to inhibit glucagon secretion, only concerns GLP-1 inhibition of glucagon secretion (see page 12). The applicants' argument is deemed unpersuasive because of the reasons stated above and the following. The reference's teaching is direct to exendin-4 not to GLP-1. The reference teaches that exendin-4 shares many of the propertie of GLP-1 and offers an obvious advantage over GLP-1 in that exendin-4 has much longer biological duration (i.e., considerablely higher *in vivo* half-time), suggeting that exendin-4 is a clinical candidate (see the first two lines) for treating disease, e.g., Type II diabetes and

inhibiting glucagon secretion. As discussed above, the glucagon suppression of glucagon secretion is an inherent mechanism of administering exendin-4 to Type II diabetes patient, and lowering plasma glucagon level is a mechanistic issue but not constitute an actual step of the claimed method. Therefore, the reference anticipates the instant claims.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is 571-272-0949. The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

SWL

Samuel W. Liu, Ph.D.

January 21, 2004

ROBERT A. WAX
PRIMARY EXAMINER